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The Oxford Handbook of Cognitive Enhancement and Brain Plasticity

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CHAPTER

Neuroscience Methods for Investigating Brain Plasticity

Luianta Verra, Fabian Renz, Nicolas Schuck

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Abstract

The brain's ability to change in response to new environments, experiences, or damage—its plasticity—is a major foundation of cognition. Unraveling the mechanisms of plasticity in humans is therefore a central goal for neuroscience. This chapter provides an overview of common methods used to study structural and functional brain plasticity in humans. The main structural methods discussed are T1-weighted magnetic resonance imaging (MRI), which is widely used to track anatomical changes in the brain, and positron emission tomography (PET), which allows investigation of neurochemical processes, such as receptor density changes. The section on functional plasticity revolves around (T2*-weighted) functional MRI (fMRI) and attempts to provide an overview of analysis methods and MRI protocols that can be used to study functional changes in the brain, including resting state, univariate, and multivariate analyses. The chapter also discusses the dynamic nature of plasticity across different timescales, spanning from single days to several weeks. The text further provides a short summary of noninvasive brain stimulation methods that, combined with other structural or functional methods, have proven to be useful tools for inducing and measuring plasticity. The chapter also addresses limitations of these methods, for tracking fast or microscopic changes, and discusses the importance of a good study design that ensures that measurements match the research question. This emphasizes the benefits of combining noninvasive brain imaging with longitudinal designs to reveal the nature of plasticity in humans.

Keywords: brain plasticity, cognition, neuroscience methods, magnetic resonance imaging, positron emission tomography, noninvasive brain stimulation

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Introduction

Our brain has considerable capacity for change. It naturally evolves across development and aging and flexibly adapts to changing demands of the environment. The term *neural plasticity* has been used to describe these

changes in the brain. Although definitions vary, most scientists agree that the term “neural plasticity” should be reserved for lasting changes that occur in response to experience or damage and have both structural and functional consequences (Lövdén, Bäckman, et al., 2010; Paillard, 1976). For this chapter, we adopt a similar definition of plasticity based on Paillard (1976, translated in Will et al., 2008), according to which a change is plastic when it involves changes in brain structure that has functional consequences (i.e., for brain activity), conversely, functional changes that induce structural change. Following this definition, not all changes in the neural system are plastic. While brief activations, such as those caused by repeatedly perceiving an object, can trigger some forms of “short-term plasticity” (e.g., synaptic potentiation; Zucker & Regehr, 2002), these changes are only temporary, and we do not consider them in this chapter. Instead, we focus on the effects of long-term plasticity, such as long-term potentiation (LTP) or long-term depression (LTD; Malenka & Bear, 2004). Structural adaptations in response to brain injuries, for instance, trigger lasting large-scale changes in brain structure and have consequences for cognitive function, and hence are an expression of plasticity. Similarly, learning a new language, childhood development, and aging all induce plasticity as the brain flexibly adapts to new demands over time. We note that in practice, it is often difficult to determine if an observed functional change results from structural changes in the brain or if the functional change precedes changes in brain structure. Analogously, observed changes in brain structures can be a cause or effect of functional changes. The methods we discuss in this chapter usually allow us to quantify functional or structural changes in the brain, but only the most carefully conducted experiments allow us to infer any direction or causality.

Timescale of Change

The ability to implement plasticity on a range of timescales is a highly desirable property for any system seeking to adapt to a complex world. A major factor determining the time scale of change is the level of neural organization. Plasticity can, for instance, affect molecular signaling (e.g., receptor expression, changes in channel density), the cellular level (e.g., myelination), or networks of cells, and each of these levels places constraints on how dynamically it can be adapted. Yet while plastic changes are by definition considered “lasting,” no general consensus on a minimum duration for a change to be considered plastic exists, with documented cases of plasticity ranging from hours to years (Miller & Constantinidis, 2024).

Broadly speaking, changes within single cells can occur in a very short timespan, but plasticity in cell networks or myelination reflects the cumulative effects of many single cell changes that may take days or even months to become apparent (Sampaio-Baptista et al., 2018). Classic examples of long-term neural plasticity include the morphological changes observed in long-time musicians and the structural differences in the hippocampi of London taxi drivers (Gärtner et al., 2013; Maguire et al., 2000), which appear to develop over years of training. On the other end of the spectrum, it has been observed that brief neural high-frequency stimulation of a few seconds can induce changes lasting several hours or days within single cells (Bliss & Lomo, 1973). This impressive potential for plasticity implies that the brain is constantly evolving in daily life, continuously forming new connections and reorganizing multiple interacting components. This makes it challenging to distinctly separate structural, plastic, and functional changes.

What We Cannot Measure (Directly) in Humans

Related to the questions about the levels at which plasticity occurs is how neuroscientists typically measure it, which poses particular challenges for human research. While this chapter largely focuses on human research, we briefly provide a summary of two core mechanisms of plasticity that have been studied mostly in animals, where neural processes can be probed invasively by directly observing individual nerve cells and where environmental, genetic, structural, and chemical factors influencing plasticity can be directly manipulated.

The first core mechanism is synaptic plasticity, which refers to changes in the strength or efficacy of synaptic transmission. The most common form of this process results from the temporal coincidence of presynaptic and postsynaptic neuronal spikes such that even brief millisecond-scale coactivations can lead to a longer-lasting potentiation or depression of synaptic connections, hence termed "spike-timing-dependent plasticity" (Caporale & Dan, 2008). Such long-term potentiation and long-term depression effects have been investigated most extensively in the CA1 region in the hippocampus, where studies have shown that experimentally induced in vivo coactivations lead to changes in synapses and in turn induce long-term and spatial memory formation (see Citri & Malenka, 2008 for overview). The second major mechanism that is difficult to study directly in humans is neurogenesis, a form of plasticity in which new neurons are generated from neural stem cells and integrated into existing neural networks. Neurogenesis occurs during development but also in the adult brain, although in this case it is spatially restricted to a few regions, including the dentate gyrus region of the hippocampus (Boldrini et al., 2018; Eriksson et al., 1998). To what extent neurogenesis persists across the life span is highly debated, but adult neurogenesis and its role in lifelong brain plasticity are exciting topics of investigation (Boldrini et al., 2018; Kempermann, 2022; Sorrells et al., 2018).

While synaptic plasticity and neurogenesis as observed in animal studies are the most foundational and best-understood aspects of plasticity, human research has focused on phenomena that reflect our natural circumstances and can be more easily studied. In the clinical domain, brain reorganization that occurs in response to trauma, for instance, is of great importance. Other commonly observed cases in humans in which brain plasticity plays a major role are more gradual and systemic. Prolonged exposure to stress, for instance, has been related to atrophy and loss of neurons in the prefrontal cortex and hippocampus (Duman et al., 2016). Relatedly, aging is characterized by widespread plasticity, including synaptic alterations in areas such as the prefrontal cortex and the hippocampus (Morrison & Baxter, 2012).

Furthermore, practical and ethical constraints on human research require much more indirect approaches that rely predominantly on noninvasive recordings such as magnetic resonance imaging (MRI) and a range of methods based on it (see below). Because the MRI signal is spatially coarse, human research mostly reflects macroscopic changes in entire cell populations, unlike the synaptic plasticity and neurogenesis mechanisms in single cells at the center of animal research. Yet, as this chapter shows, recent advances in imaging techniques have allowed us to study neural reorganization in adult humans in vivo in unprecedented detail (Chen et al., 2010). Hence, our overview of human work focuses on imaging studies of trauma, training, or environmental factors.

The remainder of this chapter is structured into five sections. First, we discuss design considerations that should be taken into account when attempting to measure plasticity, arguing that a good experimental design is essential to disentangle functional and structural components of plasticity. Next, we review methods that reflect structural brain changes, followed by an overview of functional methods. We then cover less common multimodal and neurochemical approaches. Finally, we provide some conclusions and future directions.

Design Considerations

Measuring plasticity and change inherently requires accounting for the temporal dynamics of a phenomenon of interest. Two research designs allow us to capture such dynamics to different degrees: longitudinal and cross-sectional designs. In longitudinal designs, the variable of interest is assessed repeatedly, such as before and after acquiring a new skill or at regular intervals during an intervention (e.g., training). Most importantly, the variable of interest is assessed in the same participants at each measurement point, allowing measurement of trajectories over time. Longitudinal studies are particularly suited for studying phenomena such as developmental changes but also for intervention studies such as drug trials or training studies. Alternatively, plasticity can be measured using cross-sectional designs, where individuals naturally varying in the variable of interest are assessed and compared. A cross-sectional design is often used to study changes that unfold over a long period of time and where a longitudinal design would be difficult to implement. The use of cross-sectional studies for studying change, however, has been criticized, given that their focus lies on measuring between-person differences rather than within-person change (Boker et al., 2009). Inconsistencies between longitudinal and cross-sectional results in studies investigating cognitive aging, for instance, support this position (Lindenberger et al., 2011). Here we briefly discuss the challenges and considerations of each design.

Longitudinal Study Designs

Longitudinal studies represent the gold standard in measuring plasticity as they allow us to learn about within-person change over time. However, designing and conducting longitudinal studies present multiple challenges. They are logistically demanding and require substantial resources. Additionally, various potentially confounding factors need to be accounted for, which include systematic dropout (e.g., fading motivation due to lack of improvement), changes in staff performing the study, or changes of setup (e.g., change of MRI scanner). Other confounds that potentially lead to biased conclusions are training and familiarity effects, meaning that improved performance over time might result from increased familiarity with the task rather than genuine improvement. When designing a longitudinal study, another consideration should be when and how often to measure in order to capture the change of interest (Hertzog & Nesselroade, 2003). If a change unfolds over a long period of time, measuring in intervals of months or years might be sufficient. If change is rapid, measuring in yearly distances might fail to capture the trajectory of the plastic event. The Nyquist frequency (twice the frequency with which the phenomenon of interest changes) provides a useful lower bound for such design considerations.

Cross-Sectional Study Designs

While longitudinal designs are valuable because they provide insights into trajectories of change, cross-sectional designs allow us to measure differences between groups. In cross-sectional designs, groups hypothesized to differ in a specific process—such as musical experts versus novices, or older versus younger adults—are directly compared at a single time point. This approach is beneficial in cases where longitudinal designs are infeasible. For example, the neural changes elicited by learning to play an instrument can in principle be studied longitudinally. However, tracking participants over a timespan of years, while trying to account for confounding variables, is challenging. Cross-sectional approaches allow us to contrast expert musicians with a matched control group and to measure differences at a single time point. Such designs have, for example, been used to show that musicians show differences in interhemispheric communication (Schlaug et al., 1995) or that young and older adults differ in the variability of the fMRI BOLD signal (Grady & Garrett, 2014).

However, cross-sectional designs come with their own set of challenges and limitations. Given that cross-sectional designs involve between-subject comparisons, measured change can be due to existing differences in the two groups rather than the variable assessed. One example of such differences is cohort effects, when observed differences between groups result from generational or cultural factors rather than from the variable of interest. In addition, age effects can further account for variability. Age effects include all differences that result from underlying psychological, social, or biological processes that highly correlate with age. A further critical consideration in cross-sectional designs is the causal directionality of an effect. For instance, do musicians develop different brain structures as a result of extensive training, or do individuals with certain neural characteristics become musicians because they possess the necessary predispositions? This question underscores the importance of careful experimental design and the use of complementary approaches to reveal the directionality.

Cross-sectional and longitudinal designs can be combined in what are known as *cross-sectional longitudinal designs*. This study design allows measuring groups of individuals of different ages over a period of time and conveniently combines cross-sectional with longitudinal elements. For example, Raz et al. (2005) combined a cross-sectional fMRI study with a longitudinal follow-up to investigate five-year changes in brain volume.

Choice of Control Group

One important consideration when attempting to measure plasticity, cross-sectionally or longitudinally, is the choice of control group. A *control group* is an additional group that does not receive the intervention of interest and thus contributes to causal understanding of an effect. Most importantly, control groups should be closely matched to the experimental group in all variables that are not of interest. The best way to equate possible a priori group differences is to offer so-called randomized control trials, where participants are randomly assigned to the intervention or control group (Hariton & Locascio, 2018). Furthermore, choosing an appropriate control intervention for the control group is crucial: while applying no treatment at all is a common research strategy, it raises concerns that treatment effects could reflect unintended side effects of the treatment, such as frequent social interactions that accompany a study, or retest effects. To avoid such issues, researchers often use a placebo treatment or an alternative intervention unrelated to the variable of interest. For example, in a longitudinal study, Voss et al. (2010) assessed the effect of aerobic exercise in older adults on the brain's functional connectivity. Participants were randomly assigned to the experimental or control condition, with the control condition being an alternative exercise routine based on nonaerobic exercises. Another example is the use of sham stimulation in transcranial magnetic stimulation (TMS). Given that stimulation with TMS is accompanied by a characteristic sound of the stimulation device and sensory side effects, control groups usually are administered a weak stimulation or receive stimulation of an alternative brain region that reproduces the sensory effects but that ideally does not interfere with the neural effects of the stimulation (Duecker & Sack, 2015). Besides the choice of the control group, an additional consideration concerns experimenter effects, such as preferential treatment of one group over the other. In clinical trials, this is generally prevented by designing double-blind studies, where neither the participant nor the researcher knows which treatment a participant is receiving.

In summary, measuring change requires assessing within-person trajectories, and longitudinal designs with repeated measurement points are best suited for this purpose. Cross-sectional designs provide many advantages but have to be used keeping in mind that they provide snapshots of between-person differences without informing us about change over time. The choice of design primarily depends on the phenomenon of interest and is accompanied by additional considerations around the target population and feasibility. Additional considerations when choosing a suitable design concern the choice of the control group and potentially confounding effects such as age and cohort.

Methods for Measuring Plasticity

In the next sections, we provide an overview of common methods used to measure changes in brain structure, beginning with structural MRI. We then discuss two other structural MRI–based methods, diffusion tensor imaging (DTI) and voxel-based morphometry (VBM), which can be used to study changes in white matter and gray matter, respectively. Afterward, we focus on methods used to study functional change, which include functional MRI (fMRI) and positron emission tomography (PET). Table 1 provides an overview of the considered methods and their properties.

Table 1: Overview of imaging methods discussed in this chapter. "What is measured" provides an overview of the signal measured while "Anatomical basis" describes the underlying physiological basis where a signal is believed to originate. The columns "Spatial scale" and "Data acquisition" describe the spatial resolution of the measure and the duration of signal acquisition, respectively. The values provided about time and space are approximate and should be understood as a general reference, as they are influenced by a number of factors, such as the specific hardware used for acquisition or ongoing technological developments.

Method	What is measured?	Anatomical basis	Spatial scale	Data acquisition	Invasiveness
Structural measures					
MRI-T1	Hydrogen molecule concentration	Tissue types (fat / water indicative of gray matter, white matter)	0.1–2 mm(1)	2–10 minutes	Noninvasive
DWI/DTI*	Diffusion of hydrogen molecules	White matter fiber tracts	1–5 mm(2)	4–15 minutes	Noninvasive
Functional measures					
PET	Radioactivity after radioactive tracer injection	Glucose metabolism / neurotransmitter density and activity, depending on tracer	3–10 mm(3)	30–45 minutes (plus waiting time for radiotracer absorption)	Intravenous/oral administration of radioactive tracer
fMRI*	Blood oxygenation	Metabolic demand triggered by neural activity	0.75–3 mm(4)	1–3.5 seconds per whole brain image	Noninvasive
TMS	TMS-induced changes in measure of interest (behavior / MRI)	Neural population activity (i.e., measured with EEG)	5–15 mm(5)	30–45 minutes (TMS) & 20–30 minutes (tDCS)	Magnetic stimulation

* MRI based methods;

(1) e.g., Balchandani and Naidich (2015), Feinberg et al. (2023);

(2) e.g., Holdsworth et al. (2019);

(3) e.g., Catana (2019);

(4) e.g., Uğurbil (2014, 2021);

(5) e.g., Bolognini and Ro (2010); and Sliwinska et al. (2014).

Measuring Structural Change

Structural MRI (T1-Weighted)

MRI is an imaging technique used widely to generate three-dimensional anatomical images of the brain or body in a number of ways (T1-weighted MRI is discussed here, and others are described below).

All MRI methods employ magnets that produce a strong magnetic field (B0) that forces the magnetic moment of hydrogen protons in the body to align with the field.[1] MRI is generally considered safe but given the strong magnetic field all metal objects need to be removed before scanning. Nonremovable metal bodies such as implants or pacemakers, therefore, are a contraindication for this technique. Further limitations of MRI scanning are restricted room and movement inside the scanner and noise levels during scanning.

So-called T1-weighted (T1W) MRI scans are widely used for assessments of brain structure, as they reliably indicate the relative amount of fat versus water of brain tissue in a given 3D location, known as a voxel.[2] Typical T1W MRI scans achieve a resolution on the order of 1.0 mm^3 (1 μl or 0.001 ml voxel volume), but recent developments of ultra-high-field-resolution brain imaging achieve even better spatial resolution (Balchandani & Naidich, 2015; Feinberg et al., 2023).

Voxel-Based Morphometry

A widespread analysis technique of T1W MRI data is voxel-based morphometry (VBM), in particular when researchers aim to examine changes in brain structure over time, or compare different groups of interest with high regional specificity. Unlike other analysis methods that focus on whole-brain volume or predefined regions of interest (ROIs), VBM emphasizes spatial resolution, providing a voxel-wise estimation of volume or gray matter density. This enables a detailed examination of structural differences across the entire brain and makes VBM a useful tool to study plasticity-induced structural brain changes. While typically used to assess differences or changes in gray matter density, it is also applicable to study changes in white matter, albeit with reduced sensitivity due to the homogeneity of large white matter regions (Ashburner & Friston, 2000; Kurth et al., 2015).

VBM has significantly advanced the understanding of brain structure, both in comparing different groups and in tracking plastic changes over time. For example, Sato and colleagues (2015) have used VBM to reveal gray matter volumetric differences among trained musicians when compared to hobbyists and nonmusicians, showing a positive correlation between the extent of musical training and gray matter volume. Another illustrative case is the structural adaptations associated with extensive navigation experience (Maguire et al., 2000). Using VBM, studies on the brains of London taxi drivers have demonstrated an increased volume in the posterior hippocampi, a region associated with storing spatial representations. These findings suggest that the brain has a remarkable capacity for localized plastic changes in response to environmental demands.

Diffusion Weighted Imaging and Diffusion Tensor Imaging

Diffusion weighted imaging (DWI) is another MRI-based method that measures the diffusion of water molecules in the brain. Diffusion refers to the random Brownian motion of molecules. In open water, diffusion of water molecules is random and equally probable in all directions, but the structure of the human brain, in particular its fiber tracts, restricts such molecule diffusion. These tissue-dependent differences in diffusion create image contrast that allows MRI to visualize and quantify white matter tracts in the brain. DWI is applied in medical imaging, for example, in stroke patients (Baliyan et al., 2016).

Diffusion tensor imaging (DTI) refers to a specific type of modeling DWI datasets that analyzes the three-dimensional shape of diffusion in space, known as the *diffusion tensor*. DTI provides information about the mean diffusivity in each voxel in addition to the directional preference of diffusion and diffusion rate. In white matter, the diffusion is less restricted along the axon and is directionally dependent (anisotropic). This property makes it particularly suitable for DTI modeling, allowing for the production of detailed images of white matter tracts.

DTI has been widely used as a clinical tool in the context of disorders that involve abnormalities in the brain's white matter and is increasingly used in research. It is particularly suitable to study change because it provides information about changes in the in vivo microstructure of the brain.

A study by Lövdén and colleagues (2010), for example, used DTI in combination with a training intervention, involving memory and perceptual speed tasks, to investigate plasticity of white matter tracts in the anterior corpus callosum. In their study, they further compare younger and older adults and report training effects on white matter microstructures that were comparable in magnitude across age groups. DTI has also been used to study age-related decline in white matter tracts. Voineskos and colleagues (2012), for instance, report widespread age-related changes in diffusivity of cortico-cortical white matter fiber tracts.

DWI and DTI are valuable tools to study white matter changes in the brain. The main limitations of these approaches are shared with other MRI methods and include imaging artifacts as well as complex preprocessing and analysis methods (Soares et al., 2013 for overview).

Positron Emission Tomography

Positron emission tomography (PET) is another approach that can be used to study structural plasticity in the brain. Although mainly used for clinical diagnosis of cancer, PET can be employed to study changes in blood flow and to track particular neurotransmitters in the brain (see Jones & Rabiner [2012] for overview). The main principle of PET is to first administer a radioactive tracer (often intravenously) that selectively binds to, for example, a neurotransmitter receptor or another protein, and in a subsequent PET scan detect the spatial distribution of the radioactive tracer in the brain. Common tracers in PET imaging are the glucose analogue 18F-FDG used to image glucose and oxygen-15 which provide an indirect measure of blood flow in the brain. FDG-PET studies, for instance, have revealed glucose metabolic reductions in various areas of the brain related to Alzheimer's disease, such as in areas of the cingulate cortex (Mosconi, 2005). In addition to measuring metabolic changes, PET has been used to detect changes in transmitter activity over time, such as the age-related decrease in dopamine transporters in specific brain areas in healthy subjects (Volkow et al., 1996).

Another interesting application of PET is the imaging of synaptic density by using a ligand that binds to the synaptic vesicle protein SV2A. This approach has, for example, been used to show synaptic loss in the hippocampus in patients with Alzheimer's disease (Finnema et al., 2016) and also to investigate alterations in a broad range of neuropsychiatric disorders (Cai et al., 2019).

PET imaging can be combined with MRI using specific PET/MRI acquisition systems. In such simultaneous acquisition of PET and MRI, PET can measure transmitter release, receptor occupancy, or glucose metabolism in addition to information about brain anatomy (MRI) and brain activity (fMRI) (Werner et al., 2015).

Measuring Functional Change

Functional magnetic resonance imaging (fMRI) builds on MRI technology and allows for measuring changes in brain activation through the blood oxygenation level dependent (BOLD) effect (Hillman, 2014; Ogawa et al., 1990). The BOLD signal results from neural activity increasing oxygen consumption, which triggers a local increase in blood flow through mechanisms known as *neurovascular coupling*. This blood flow response causes an increase in (diamagnetic) oxyhemoglobin and a decrease in (paramagnetic) deoxyhemoglobin that leads to magnetic field distortions that fMRI can measure. While the BOLD signal is an indirect measure of brain activity (Poldrack, 2000), it offers great opportunities to study plasticity-induced functional changes noninvasively in the human brain.

Functional Connectivity and Resting State

Functional connectivity refers to similarities in brain activations and synchronization of brain regions and is assessed by measuring systematic coactivations between voxels, the spatial units of measurement in MRI. These coactivations build "functional" networks that are often closely aligned with anatomical structures, such as the default mode network (Guerra-Carrillo et al., 2014). Generally we can distinguish between resting-state connectivity and task-based connectivity. Resting-state functional connectivity (rs-FC) measures spontaneous fluctuations in brain activity when a participant is not engaged in a specific task. To examine plasticity, rs-FC before and after an intervention are contrasted to capture experience-dependent plastic changes. A notable example is the study by Newbold and colleagues (2020), in which participants' dominant arms were immobilized in a cast for two weeks, inducing motor deprivation. Using daily resting-state fMRI scans, it was shown that cortical and cerebellar regions associated with the immobilized limb disconnected from the broader motor network within forty-eight hours. Interestingly, the internal connectivity within the unused subcircuit remained intact, and large spontaneous activity pulses were observed—suggesting a protective mechanism to preserve existing connectivity. Critically, these changes were reversible: after the cast's removal, the previously disconnected regions gradually reintegrated into the motor network, with functional connectivity returning to baseline levels within days. This study provides compelling evidence of the adult brain's plastic capacity and demonstrates how fMRI can effectively capture plastic changes in functional connectivity in the human brain.

In rs-FC studies, plastic changes are often tracked longitudinally, with pre- and postintervention comparisons over weeks or months (Guerra-Carrillo et al., 2014; Powers et al., 2012; Vahdat et al., 2011). However, researchers increasingly explore ways to track plastic changes on shorter timescales, such as during learning or memory formation, within individual experimental sessions (Taren et al., 2017; Yuan et al., 2014).

In addition to resting-state measures, functional connectivity can be assessed while participants actively perform a task, using so-called task-based functional connectivity measures. In a study by Allegra and colleagues (2020), functional connectivity was assessed continuously while participants performed a perceptual decision task where they had to identify the dominant direction of motion of a random dot cloud. During the task, dot color became related to the response, meaning that participants could switch strategy to successfully solve the task. On-task connectivity measures revealed differences in connectivity when comparing periods of strategy optimization and strategy change, showing a clear example of short-term, on-task network plasticity.

A variety of analytical tools are used to contrast different experimental conditions or track changes in neural activation over time. For a more detailed overview, we point to the chapter on Network Neuroscience Methods for Investigating Brain Plasticity in this textbook.

Univariate Analysis

Univariate analysis is one of the most commonly employed methods for examining brain function and has been successfully applied to track changes in neural activation. For example, Moody and colleagues (2004) provided evidence of a compensatory shift in neural activity in Parkinson's disease patients. Specifically, as a result of diminished striatal function caused by their disease, patients exhibited increased recruitment of the medial temporal lobe (MTL) during an implicit learning task. This compensatory activation suggests an interaction between memory systems involving the MTL and striatum. Similarly, Poldrack and colleagues (2001) demonstrated a dynamic nature of memory system engagement during learning in healthy participants. Their findings revealed a shift from early-stage learning, which primarily engages the MTL, to later stages where MTL involvement decreases as the striatal system becomes increasingly recruited, reflecting a transition from declarative to procedural learning. Using univariate model–based fMRI, Schuck and colleagues (2015) showed in a spatial navigation task that, compared to younger adults, older participants showed a shift toward more striatal activity that was related to processes linked to the MTL in younger adults. This suggests that a dynamic interplay of neural resources linked to memory is altered by age-related structural changes, in line with a wider line of research on such shifts in aging (Zahodne & Reuter-Lorenz, 2019). In combination, these studies show how univariate techniques can reveal plasticity-induced changes in recruitment of neural resources—either compensating for impaired functionality or, in healthy participants, reflecting a dynamic shift in brain region engagement over the course of learning and memory formation.

A more recent approach for studying brain plasticity with fMRI is repetition suppression, also known as fMRI adaptation. This method capitalizes on the observation that neurons exhibit reduced responses to repeated presentations of the same stimulus, a phenomenon interpreted as a marker of increased neural efficiency (Grill-Spector & Malach, 2001). The physiological basis for repetition suppression was first identified in primates, where neurons in the inferotemporal cortex showed decreased activity with repeated exposure to the same visual stimuli (Barron, Garvert, et al., 2016). This suppression effect, now documented across various brain regions and types of stimuli, reflects a general neural coding mechanism by which the brain optimizes its response to repeated information.

Repetition suppression has emerged as a pivotal method for examining how neural representations are fine-tuned through repeated exposure in human research. In an interesting study, Barron and colleagues used repetition suppression to track the formation of associated memories after a short learning session, and also showed that such markers of plasticity can disappear soon thereafter due to a process of inhibitory rebalancing, which presumably happens overnight (Barron, Vogels, et al., 2016). This study thereby demonstrates how functional measures can provide important insights into the complex nonlinear dynamics of plasticity, which previously also have been documented using structural measures (Wenger et al., 2017). Repetition suppression has also revealed adaptations to the experienced structure of the environment that occur on short time scales. Garvert and colleagues (2023) observed a cross-stimulus enhancement effect—essentially an inverted form of suppression—emerging during a choice task, where this enhancement scaled with spatial distance between stimuli. This effect indicates that participants updated their cognitive maps in response to reward prediction errors encountered throughout the task.

Representational Similarity Analysis

A final set of analysis techniques applied to fMRI that has proven useful for studying plasticity comes from multivariate pattern analysis (MVPA) approaches.

Here, one prominent approach is representational similarity analysis (RSA), which compares activity patterns across conditions or time points by quantifying their similarity. A core strength of RSA is that by focusing on a neural similarity space, it abstracts from many details of the neural recording (e.g., timescales or how many units were recorded). This allows researchers to compare results across vastly different systems—for instance, between animal electrophysiology and human fMRI, or between human neural activation patterns and simulated computational models of brain function (Kriegeskorte et al., 2008).

An illustrative example of using RSA to track representational changes over time comes from Bellmund and colleagues (2019), who investigated how the lateral entorhinal cortex (lEC) represents temporal structure. In this study, participants learned temporal and spatial relationships between objects encountered along a fixed route in a virtual city. By comparing multivoxel pattern similarity before and after the learning task, Bellmund and colleagues (2019) demonstrated that learning altered the neural representations of objects in lEC, such that they reflected the temporal structure of the task. This approach highlights how the entorhinal cortex evolves to map temporal structure in response to experience.

Another multivariate fMRI analysis technique is the application of classification algorithms that can detect the presence or strength of activity patterns associated with particular stimuli. Using this approach, Shibata and colleagues (2012) could, for instance, show that motion detection training leads to better classification of direction signals in the visual cortex. In another study, Atir-Sharon and colleagues (2015) have shown that pattern classifiers can be used to predict future performance in a semantic associative learning task, enabling the tracking of rapid plasticity processes that underlie such learning. In yet another study, Schuck, Gaschler, and colleagues (2015) used decoding to predict which participants would learn a visual-motor association before it was evident in behavior, indicating that MVPA can be used to identify plasticity processes.

In conclusion, fMRI provides a powerful method for studying brain plasticity, especially in longitudinal studies. Recent advances in techniques such as RSA, repetition suppression, and pattern classification have significantly expanded our ability to detect dynamic changes in neural activity patterns, offering deeper insights into core cognitive functions such as learning and memory.

Noninvasive Brain Stimulation: TMS and tDCS

The final key addition to the arsenal of methods for studying brain plasticity that we want to discuss is noninvasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS). These methods are not about measuring plasticity but rather can induce plasticity by interfering with and stimulating neural activity in the brain.

In TMS, a specific coil is used to produce a magnetic field that penetrates the scalp, inducing a flow of electric current that stimulates the underlying tissue (Bestmann, 2008). Stimulation is generally limited to superficial areas of the cortex and can be of excitatory or inhibitory nature. The exact mechanism underlying TMS is, however, a matter of active debate (Siebner et al., 2022). tDCS in contrast uses weak direct electrical currents that are continuously applied to the scalp between two sponge electrodes. tDCS is thought to change the resting membrane potential of neurons, causing lasting changes in cortical-evoked potentials.

TMS and tDCS can both be applied offline (before a specific task is administered) or online (during the task). Depending on the stimulated area, stimulation-induced changes in neural activity can have behavioral effects, such as changes in reaction times (Marshall et al., 2005) or motor responses (Saucedo Marquez et al., 2013). In a study using TMS to investigate effects on language, for instance, Devlin and Watkins (2007) showed how TMS can induce so-called speech arrest when stimulating areas of the scalp corresponding to the left inferior frontal cortex. In this study, subjects were asked to count aloud and TMS stimulation resulted in subjects being unable to proceed with counting (Devlin & Watkins, 2007; Pascual-Leone et al., 1991). This shows how TMS can induce a "virtual" temporary lesion that is consequently expressed in behavioral changes and thus might help understand the plasticity processes that underlie real lesions.

To better understand the neural changes induced by TMS or tDCS, researchers often concurrently measure brain activations using imaging methods discussed above, such as EEG, PET, or fMRI. Koolschijn and colleagues (2019), for instance, used tDCS stimulation in combination with imaging and computational modeling to show how neural inhibition plays a role in protecting memories from interference. In their study, participants learned two overlapping but context-dependent memories and fMRI was used in combination with RSA analysis to measure the neural representations and behavioral interference of these two memories. Next, tDCS was applied to decrease the release of the neurotransmitter gamma-aminobutyric acid (GABA) in interneurons which has been associated with neural inhibition. The decrease of GABA was measured using noninvasive magnetic resonance spectroscopy (MRS). The authors found that tDCS-induced reduction of GABA was associated with more interference between two overlapping memories, indicating that GABA and neural inhibition play a role in gating learning and memory (Barron, 2021; Koolschijn et al., 2019). Other examples of concurrent brain stimulation and functional imaging are a range of studies showing the effects of focal stimulation on neural network activity. Using TMS, for instance, Hartwigsen (2018) has shown that virtual lesions of specific brain areas lead to up- or downregulation of activity in other areas of a network—a phenomenon that has been interpreted as a flexible compensation mechanism (Hartwigsen, 2018).

Single stimulation sessions are thought to produce transient activation changes, lasting approximately one hour. In addition to short-term changes, more persistent changes have been reported for repeated stimulation (Monte-Silva et al., 2013). Substantial variation in the responses to TMS or tDCS stimulation has been reported, highlighting the need for further research into factors undermining stimulation effectiveness (López-Alonso et al., 2014; Vergallito et al., 2022).

Recent developments further see the use of TMS and tDCS to treat chronic pain (Lefaucheur et al., 2008) or in language therapy to promote language recovery in poststroke aphasia (Hamilton et al., 2011; Hartwigsen & Volz, 2021).

Open Questions and Future Directions

The brain has an extraordinary capacity for reorganization in response to changing internal and external demands. This plasticity can be observed across a range of contexts, from spontaneous recovery following damage such as stroke or injury, to training-induced adaptations that occur over extended periods. Neural plasticity occurs across multiple levels of neural organization, ranging from microscopic molecular signaling changes to macroscopic adaptations in large-scale neural networks. The timescales of these plastic changes vary significantly, from rapid changes within seconds or minutes on a microscopic level (such as LTP), to long-term structural adaptations and functional reorganization that unfold over hours, days, and years. While invasive animal studies can directly examine mechanisms such as synaptic plasticity and neurogenesis at a finely resolved scale in time and space, noninvasive imaging and analysis methods available in humans only access mostly macroscopic changes on slower timescales. Furthermore, they measure the biological processes indirectly—for instance, by tapping into magnetic changes that track alterations in blood flow. Despite their indirectness, modern-day techniques such as MRI and PET have provided unparalleled access to brain plasticity and the many ways in which it manifests in the brain and behavior. Over the past decades we have also witnessed a continued and significant improvement of our capacity to capture dynamic changes in the human brain. Here, we have sought to provide an overview of many recent developments in the study of neural plasticity in humans. We highlighted the diversity of analytical approaches that researchers have employed and continue to develop. Innovative approaches that have shed light on the multifaceted nature of plasticity include functional connectivity studies, VBM, RSA, or multivariate decoding techniques. We have also provided examples of studies that have integrated noninvasive brain stimulation methods, such as TMS and tDCS, with neuroimaging, showcasing the potential for studying plasticity by enabling temporary, reversible perturbations and causal inference about brain function. Pairing these techniques with refined analysis tools and improving neuroimaging should enable a better understanding of neural plasticity and support its clinical applications. Here we have covered some examples of studies that have used sophisticated designs to advance our understanding of plastic long term changes in humans. Newbold and colleagues (2020), for instance, used daily fMRI resting-state scans to show how restriction of arm movement can result in rapid reorganization of functional connectivity; Koolschijn and colleagues (2019) used a tDCS intervention in combination with magnetic resonance spectroscopy and fMRI representational similarity analysis to show how neural inhibition protects memories from interference.

We also highlighted that measuring within-person change requires careful consideration of the study design, which ultimately determines and limits what we can measure. We have highlighted in particular how the study of plasticity calls for repeated within-person measurements, and have provided examples where such designs have provided valuable contributions to our understanding of plasticity.

There are promising ongoing developments in the field that we have not covered in this chapter. Real-time neurofeedback (rtNFB) is one newly emerging technique, which allows researchers to provide live feedback to participants about their brain activity during the experimental session, with the goal to train the ability to one's own brain activity (Sitaram et al., 2017). rtNFB has been applied to a variety of phenomena ranging from attention to memory and motor control among others (deBettencourt et al., 2015; Scharnowski et al., 2015). Sulzer and colleagues (2013) provide an overview of the field, discussing progress and current limitations of rtNFB. Another recent advancement is transcranial ultrasound stimulation (TUS), which has expanded the toolkit for noninvasive brain stimulation. TUS offers enhanced spatial precision, which makes it particularly promising for targeting specific neural circuits with greater accuracy. Emerging evidence suggests that TUS may promote neurogenesis, adding a potentially powerful approach for stimulating brain plasticity (Qin et al., 2024). Another promising line of methodological advancement is the development of ultra-high-field MRI and combined PET-MRI. These technologies offer improved spatial resolution and greater detail on molecular and structural changes, thereby reducing the gap between invasive animal studies and noninvasive human research. Ultra-high-field MRI allows researchers to detect subtle structural changes in the brain that are associated with plasticity (Zsido et al., 2023), while PET-MRI enables simultaneous acquisition of structural and molecular data, providing more comprehensive insights into the biological underpinnings of plasticity. Noteworthy progress is also being made in neuroimaging analyses. Of particular interest are studies focusing on neural replay, the fast sequential reactivation of neural activity patterns that is thought to play an essential role in consolidation, and thereby plasticity (Wittkuhn et al., 2021). Replay was originally identified in animal studies and long thought to be inaccessible with current techniques in humans. Thanks to advances in both magnetoencephalography (Liu et al., 2019) and fMRI (Schuck & Niv, 2019; Wittkuhn & Schuck, 2021) analysis techniques, replay is now increasingly studied in humans (Liu et al., 2022).

Notes

1 Protons naturally spin on their axis, behaving like magnets themselves. When aligned with B0, they create a net magnetization called M0. For imaging, short radio-frequency pulses are applied to stimulate the protons, causing them to go out of phase and the magnetization to tip away from B0. MRI sensors then capture the energy released from protons once they realign with the magnetic field. During this process of relaxation, the magnetization at each time point can be described as the *recovered longitudinal magnetization along B0* (T1) and the *remaining transverse magnetization that decays exponentially to 0* (T2). Different tissues such as fat or water have different relaxation times, which in combination with a suitable pulse sequence, can be exploited to create image contrast.

2 T1W MRI leverages differences in longitudinal magnetization times between fat and water.

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